UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/932,483	08/17/2001	Katalin Veronika Lukacs	12071-010002	5360

22442 7590 03/27/2006

SHERIDAN ROSS PC
1560 BROADWAY
SUITE 1200
DENVER, CO 80202

EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 03/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/932,483	LUKACS ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6,7,14-31,33,39,40,53 and 54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6,7,14-31,33,39,40,53 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 2/01/06 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendments, remarks, and IDS, filed 2/01/06, have been entered.

2. Claims 1, 2, 4, 6, 7, 14-31, 33, 39, 40, 53, and 54, are pending and being acted upon.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 2, 4, 6, 7, 14-31, 33, 39, 40, 53, and 54 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth previously, A review of the art shows that little is known about the use of heat shock proteins for the treatment of eosinophilic inflammatory responses. There are some teachings that the administration of certain mycobacteria can be used to treat allergic responses, but the active component of the mycobacteria is not known. Accordingly, the specification must be looked to for guidance in the instant case. A review of the specification discloses that the method of the instant claims presumably treats Th2 mediated diseases by administering a heat shock protein to skew the immune response towards Th1. This method is, again presumably, based on the theory that there exists a Th1/Th2 balance wherein increasing the Th1 or Th2 response decreases the other. The experiments disclosed in the specification show that *M. leprae* HSP-65 can induce a T cell response and that administration of *M. leprae* HSP-65 before induction of airway hyperresponsiveness, in a mouse model, can abolish said hyperresponsiveness. Curiously, it is noted that whereas source and grade of other reagents such as ovalbumin is disclosed, the one reagent absolutely critical to the claimed method, the HSP, is merely disclosed as *M. leprae* HSP-65 in PBS, provided by Inventor Lukacs.

First note that many investigators consider the Th1/Th2 paradigm an overly simplistic way to view highly complex systems. See for example Louzoun et al. (2001)

wherein the authors attempt to develop a mathematical model to account for contradictory results often seen in attempts to skew the Th1/Th2 ratio, e.g., enhancement (rather than the predicted suppression) of a Th1 mediated disease by the induction of a Th2 response. The authors conclude that Th1 and Th2 cells are more likely markers than effectors in certain diseases. Other authors have concluded that attempts to skew the Th1/Th2 ratio might be dangerous, see for example Brunet et al. (2002).

Even assuming the truth of the Th1/Th2 paradigm, the minimal disclosure of the specification is insufficient given the breadth of the claims. Note that many of the diseases specifically recited in the claims cannot be considered to be strictly Th2 mediated. See, for example, Shimada et al., which teaches that both Th1 and Th2 cytokines play a role in the development of atopic dermatitis. Clearly, simply increasing the Th1 response would not likely provide an effective treatment for this condition. Nance et al. teaches that the interstitial lung disease hypersensitivity pneumonitis is Th1 mediated. Again, increasing the Th1 response would not likely provide an effective treatment for this condition. Also see Mandic et al. which teaches that intrinsic asthma is also called nonallergic asthma (as opposed to extrinsic, allergic, asthma); it is unlikely that increasing the Th1 response would provide an effective treatment for this nonallergic (and non Th2 mediated) condition either.

Also note that not all heat shock proteins comprise the same immunological activities. Even the Inventor's own work, Rha et al. (2002), teaches that of 5 HSPs tested, only an unidentified *M. leprae* HSP had any immunological activity. It must also be noted that many investigators have found that the administration of HSPs can actually *induce* a Th2 response, see for example Francis et al. (2000).

Clearly then, the limited disclosure of the instant specification is insufficient support for the methods of the instant claims. In view of the quantity of experimentation necessary, the lack of sufficient working examples, the unpredictability of physiological activity, and the lack of sufficient specific guidance in the specification, it would take undue trials and errors to practice the claimed invention.

Two issues remain. First, looking to the complete response to Brunet et al. by Wohlleben et al., the authors state, "We agree totally with Rosa Brunet et al. that any vaccine that induces allergen-specific T helper 1 (Th1) responses has the potential for serious side-effects and therefore, cannot be used in humans at present. However, to date, this issue has not been resolved clearly and we feel that more research is needed before reaching the conclusion that the induction of allergen-specific Th1 responses should be discarded totally as a potential approach to anti-allergy vaccination." It is clear that in 2002, at least Burnet et al. and Wohlleben et al. were not of the opinion that the induction of a Th2 response *in vivo* was an acceptable treatment for allergy. While the idea might have potential, the idea did not rise to the level of invention.

One other issue also remains. As set forth previously, in all experiments disclosed in the specification, the therapeutic formulation, i.e., *M. leprae* HSP-65, was administered before the induction of disease, i.e., airway hyperresponsiveness or eosinophilia. Thus, there is no evidence of record that the method of the instant claims could be used to reduce an ongoing inflammatory response, i.e., a method that would be encompassed by the method of the instant claims.

Applicant's arguments, filed 2/01/06, have been considered but they have not been found persuasive. Applicant argues that, "with regard to the issue of Burnet [*sic*] et al., the only

stated or implied basis for the Examiner's enablement rejection in view of Burnet[*sic*] et al. (with further reference to Wohlleben et a1.) is based on the allegation that such a therapy might be dangerous because it could lead to Thl-mediated pathology, rather than cure the allergy ... the Examiner's rejection on this point relates to an alleged issue of safety to the patient. However, Applicants submit that both the Patent Office and the courts have long held that the Patent Office should confine its review of patent applications to the statutory requirements of the patent laws, and that the issue of safety is not a sufficient reason to reject a claim on the basis of enablement".

In citing Brunet et al. (Applicant first cited Wohlleben et al. in response to the Examiner's citing Brunet et al.) the Examiner was establishing that the concept employed in the method of the instant claims, i.e., the manipulation of the Th1/Th2 balance, was still considered so dangerous, some 4 years after the priority date of the instant application, as to comprise only an idea and not an invention. Applicant rightly points out that the Office is not "assigned the responsibility of ensuring conformance to standards established for the advertisement, use, sale or distribution of drugs", it is however, the Office's responsibility to assess whether or not a concept has risen to the level of invention. In this instance it is not an issue of evaluating adverse side effects, but rather an issue of evaluating whether or not the very concept by which the invention of the instant claims might function is valid. In this instance, while Brunet et al. have discarded the concept, even Wohlleben et al. admit that, at best, more research is need before reaching any conclusions. Accordingly, it remains the Examiner's position that the manipulation of the Th1/Th2 balance for the treatment of any sort of disease comprises no more than an unproven idea and certainly not an invention.

Applicant argues, "with regard to the issue of when the heat shock protein is administered, Applicants initially note that the HSP was administered to the animals after allergic sensitization, but before the actual induction of an acute airway response (constriction), for example, using methacholine (a stimulus). Therefore, the HSP was not administered before induction of the disease, but rather before induction of an acute response in an animal that was already sensitized to the allergen".

Applicant appears to be splitting technical hairs with this argument. It remains the Examiner's position that the treatment was administered before the induction of any symptoms thus, the model employed by Applicant is not representative of the method of the instant claims.

Applicant argues, "Airway inflammation and airway hyperresponsiveness (AHR) are not single episodes in a patient with an allergic inflammatory disease, but rather, these are ongoing conditions that are associated with the disease … a patient can have ongoing or chronic AHR but not presently be experiencing an acute episode of airway hyperresponsiveness, or bronchoconstriction or airflow limitation, as occurs in response to a stimulus … only a "reliever", such as a bronchodilator, can reverse the immediate constriction in an acute attack of airway constriction in a patient that has AHR. The treatment of the present invention represents a second type of control over AHR, which can be referred to as a "controller". A controller acts to reduce the occurrence, severity or frequency of the episodes of acute bronchoconstriction in a patient, thus reducing or preventing AHR in the patient".

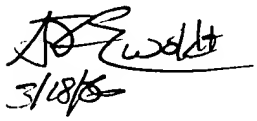
Applicant's argument would appear to be that the method of the instant claims works only when the patient is not actually suffering from AHR. Such a method would seem to require a rejection under 35 U.S.C. 101. Further, the specification provides essentially no evidence that the claimed method would operate to "reduce the occurrence, severity or frequency of the episodes of acute bronchoconstriction in a patient, thus reducing or preventing AHR in the patient" as Applicant asserts because none of these disease parameters were measured in a model simulating an AHR patient. In the instant model the experimental mice were not yet AHR patients, i.e., they mice had not yet experienced AHR, when treated.

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina

Chan can be reached on (571) 272-0841.

7. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



3/18/06

G.R. Ewoldt, Ph.D.
Primary Examiner
Technology Center 1600